

openheart Caseload management and outcome of patients with aortic stenosis in primary/secondary versus tertiary care settings – design of the IMPULSE enhanced registry

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ABSTRACT

Background Severe aortic stenosis (AS) is one of the most common and most serious valve diseases. Without timely intervention with surgical aortic valve replacement or transcatheter aortic valve replacement, patients have an estimated survival of 2–3 years. Guidelines for the treatment of AS have been developed, but studies suggest that as many as 42% of patients with AS are not treated according to these recommendations.

The aims of this registry are to delineate the caseload of patients with AS, outline the management of these patients and determine appropriateness of treatments in participating centres with and without onsite access to surgery and percutaneous treatments.

Methods/design The IMPULSE enhanced registry is an international, multicentre, prospective, observational cohort registry conducted at four central full access centres (tertiary care hospitals) and at least two satellite centres per hub (primary/secondary care hospitals). An estimated 800 patients will be enrolled in the registry and patient follow-up will last for 12 months.

Discussion In addition to the primary aims determining the caseload management and outcome of patients with AS in primary, secondary and tertiary care settings, the registry will also determine a time course for the transition from asymptomatic to symptomatic status and the diagnostic steps, treatment decisions and the identification of decision-makers in tertiary versus primary/secondary care hospitals. The last patient will be enrolled in the registry in 2018 and results of the registry are anticipated in 2019.

Registration number NCT03112629.

BACKGROUND

Aortic stenosis (AS) is one of the most common and most serious valve diseases. The prevalence of AS increases with age, affecting approximately 0.2%, 1.3%, 3.9%

Key questions

What is already known about this subject?

- ▶ Severe aortic stenosis (AS) is one of the most common and most serious valve diseases. With the onset of AS related symptoms, patients have an estimated survival of 2–3 years without timely intervention with surgical aortic valve replacement or transcatheter aortic valve replacement.
- ▶ Despite the availability of guidelines for the treatment of AS studies have reported non-adherence to these guidelines with up to 42% of AS patients not being treated according to these recommendations.

What does this study add?

- ▶ The registry will be used to outline the current management of patients with AS and determine the adequacy of treatment with and without onsite access to surgery and percutaneous aortic valve replacement.
- ▶ Information will be collated about the time course for the transition from asymptomatic to symptomatic status, diagnostic work up, treatment and the identification of decision-makers in tertiary versus primary/secondary care hospitals.

How might this impact on clinical practice?

- ▶ The aim of the registry is to optimize clinical care pathways of AS and patient's outcome in primary, secondary and tertiary care hospitals.
- ▶ In patients with transition from asymptomatic to symptomatic AS, identification of predictors and potential triggers for rapid progress of AS will probably help to provide patients with better treatment options in the future.

and 9.8% of patients aged 50–59 years, 60–69 years, 70–79 years and 80–89 years, respectively.¹ In Europe, it is estimated that there are approximately 4.9 million patients

over 75 years with AS and 1.0 million patients with severe AS.¹

AS is characterised by a narrowing of the aortic valve opening, restricting blood flow from the left ventricle to the aorta and potentially affecting pressure in the left atrium and the pulmonary circulation. Eventually, with progression of stenosis severity, patients will develop symptoms of angina (35% of patients), syncope (15% of patients) or dyspnoea and/or heart failure (50% of patients), which without timely surgical intervention, result in an average survival of 2–3 years and are associated with an increased risk of sudden death.^{2–4} Treatment options for patients with severe AS include surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR).^{5–7}

In 2017, the European Society for Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) published guidelines for the management of valvular heart disease (VHD), which recommend intervention with SAVR or TAVR in patients with severe AS, with the exception of patients with severe comorbidities where intervention is unlikely to improve either their quality of life or their chances of survival.⁸ For asymptomatic patients with severe AS, intervention with SAVR is recommended if the patient has left ventricular ejection fraction (LVEF) <50%, is physically active, or have the presence of risk factors (very severe AS, relevant progression, markedly increased levels of B-type natriuretic peptide (BNP) or severe pulmonary hypertension attributed to AS) and a low individual surgical risk.⁸

Several studies have reported non-adherence to guidelines in clinical practice and cite discrepancies between treatment decisions and the current scientific recommendations occurring in 23%–42% of patients with AS.^{9–13} Non-adherence to guidelines involved ‘overuse’ and ‘underuse’ of interventions for AS, as well as insufficient diagnostics to make an informed treatment decision.¹³

The precedent IMPULSE registry, which evaluated the current practise of SAS patients showed that there is a high rate of delayed intervention across Europe: almost 20% of the patients assigned to TAVR or SAVR failed to receive intervention within 3 months. Furthermore, valve replacement was also performed in asymptomatic patients.¹⁴

However, there is a lack of data regarding the management of these patients in smaller centres and practices which do not have the possibilities to perform TAVR/SAVR in-house.

Thus, the aims of the IMPULSE enhanced registry are to determine the difference in the management and treatment of patients with AS in primary, secondary and tertiary care hospitals. Furthermore, the registry will collect data on whether the presence of symptoms of AS affects the manner in which a patient is monitored and treated and, finally, it will determine the time course for the development of symptomatic AS.

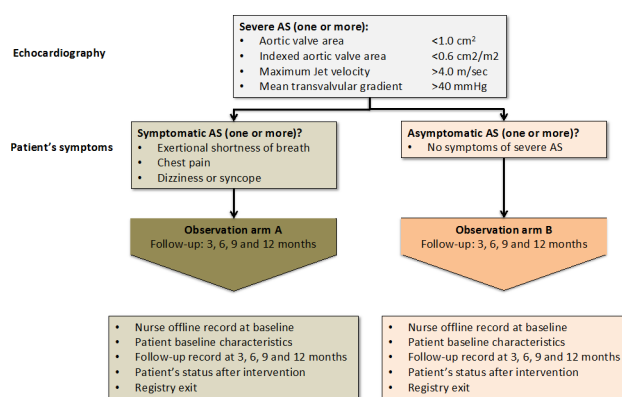


Figure 1 Overview of IMPULSE enhanced. The IMPULSE enhanced registry will recruit 800 subjects with AS diagnosed by echocardiography. Subjects will be divided into either symptomatic or asymptomatic AS. A nurse will record subject information into an eCRF. Subject follow-up will take place every 3 months. Information on the patient's status after intervention and their reason for exiting the registry will be recorded. AS, aortic stenosis; eCRF, electronic case report form.

REGISTRY DESIGN

IMPULSE enhanced is a multicentre, multinational, observational, prospective registry designed to delineate the case load of patients with AS, outline the management of these patients and determine the appropriateness of treatments in participating centres with and without onsite access to surgery and percutaneous treatment (Hub: tertiary care centre; Satellite: primary or secondary care centre) (figure 1). The registry aims to enrol at least 800 patients consecutively over a 9-month recruitment phase, at four hubs (two hubs in Germany and one hub each in France and the UK) with at least two satellite centres per hub. The registry is established in accordance with the Declaration of Helsinki (1964), and prior ethical agreements have been obtained from the appropriate ethics committee at each site. Prior to enrolment, patients are required to provide informed consent and data are collected by a co-ordinating nurse in the form of electronic case report forms (eCRFs).

Participating sites

Patient recruitment will take place at the following hubs (tertiary care centres)—Kiel and Cologne (Germany), Paris (France) and Birmingham (UK). Each hub centre will select at least two satellite centres (referred to as secondary care centres) within a 30-mile/50-kilometre distance that has no onsite access to AS interventions. These sites are usually defined by the presence of an office-based cardiologist; there were no general practitioners involved into the study as a secondary care centre. At each site, three different groups of personnel will be involved—physicians referring patients for echocardiography, echocardiography technicians/physicians and a nurse for data acquisition.

Patient selection

To be included in the registry, patients must be aged 18 years or older and have a new diagnosis of severe AS made by transthoracic echocardiography. Severe AS is defined as one or more of the following criteria—aortic valve area of <1 cm, indexed aortic valve area of <0.6 cm², maximum jet velocity of >4.0 m/s and/or mean transvalvular gradient of >40 mm Hg. Patients not complying with the inclusion criteria, those with a diagnosis of non-severe AS and patients with previous AVR will be excluded from participation.

Data collection

All patient data will be captured on an eCRF (Software for Trials Europe GmbH, Berlin, Germany) and signed by the documenting nurse. Patient anonymity will be maintained through the use of a patient registry identifier number. Automatic checks for plausibility and completeness of patient records will be performed, and the data manager will examine all data sets for irregularities. Any amendments to the eCRFs will be documented. All data sets will be submitted for biostatistical analysis.

In addition to recording inclusion criteria, patient-related variables (patient consent, age, gender, weight, in-patient/out-patient status), physician-related variables (whether the patient was referred by a cardiologist/cardiologist, cardiac surgeon, non-cardiologist/general practitioner or other specialist) and patient baseline characteristics will be recorded. These include echocardiography data at baseline, medical history/symptoms at baseline (including details of aortic valve-related symptoms), comorbidities and a risk assessment based on the European System for Cardiac Operative Risk Evaluation I (EuroSCORE I, mandatory) and the EuroSCORE II and/or the Society of Thoracic Surgeons (STS) Score (optional). Frailty will be assessed at baseline and classified as none (definition: able to walk 5 m in under 6 s plus independent Activities of Daily Living (ADL, wash dress feed; toilet)), mild (definition: unable to walk 5 m under 6 s or fails to perform one ADL) or severe (definition: unable to perform 2 or more ADL). There is no validation of the primary diagnosis of severe AS by an independent qualified person as we felt that the heart team preparing a potential intervention would in any case reconfirm and thus validate the diagnosis.

The main follow-up will be performed for all patients at 3, 6, 9 and 12 months by the documenting nurse contacting the referring physician (primary contact for the patient). Contact will be made by either telephone, email/fax or letter. For patients who had symptomatic AS at baseline, information on the treatment they received, who made the decision to treat and where the patient was treated at which date (tertiary vs primary/secondary care centre) will be recorded. The lead time will be determined by subtracting the date of the final intervention (SAVR or TAVR) from the baseline visit where the new diagnosis of severe aortic stenosis is made. For patients with asymptomatic AS at baseline, information on the

patient's status (alive or dead, and if the latter the cause of death), which tests were performed after the initial echocardiogram, adverse events since previous visit, details of interventions performed and their rationale, who made the decision to perform treatment and where the patient was treated will be recorded. If patients with asymptomatic AS at baseline received no intervention, then information about patient symptoms at follow-up and further echocardiograms will be recorded. The eCRF will also record information on the patient's status after intervention and the reason for the patient exiting the registry.

Exploratory objectives

The overall objective of the registry is to compare the caseload management and outcome of patients with AS in tertiary versus primary/secondary care hospitals and the appropriateness of patient management and follow-up. The registry is also designed to determine whether patient presentation (patients displaying asymptomatic or symptomatic AS) affects their treatment and management. The primary objective of the registry is to determine the difference in patient treatment and management in tertiary versus primary/secondary care hospitals including the diagnostic steps, treatment decisions and identification of decision makers in the primary/secondary versus tertiary care settings.

Statistical analyses

The registry aims to enrol approximately 600 patients at the hubs (tertiary care hospitals) and 200 patients at the satellite centres (secondary care centres) during the observational period, which will enable exploration of the data set with enough power to determine prevalence rates with a narrow CI and to observe transitions from asymptomatic to symptomatic AS in sufficient cases to draw solid conclusions. Based on previous experience with the topic, we estimate that 22% (95%CI 3.31 for 600 patients) of patients at the hubs will not undergo valve replacement despite being diagnosed with severe symptomatic AS. If patients are asymptomatic but have severe AS, the rate is 55.6% (95%CI 3.98 for 600 patients). As physicians in the hub have every treatment option available, we assume that the rate of patients not undergoing valve replacement is higher in primary/secondary care facilities where other 'watch and wait' aspects may influence decisions. If we assume that the rates for conservative treatment are 40% (95%CI 6.79 for 200 patients) for symptomatic and 75% (95%CI 6.00) for asymptomatic patients at the primary/secondary care facility, we would be able to confirm the difference as CIs will not overlap.

The intention-to-treat analysis will include all patients enrolled in the registry. Descriptive data summaries will be used to present and summarise the collected evaluation data. Frequency distributions will be provided for categorical variables (eg, gender). For numeric variables (eg, patient age) the minimum, maximum, mean, median and SD will be calculated by Kaplan-Meier analyses to

determine survival outcomes. Where applicable, univariate and multivariate analyses will be performed.

DISCUSSION

In the present international, multicentre, prospective, observational registry, the aim is to gather data on the impact of managing and/or treating patients with severe AS at primary, secondary and tertiary care centres in Europe. The level of information captured on the eCRF forms will also allow determination of the appropriateness of treatments, the time course for the development of symptomatic AS and the identification of key decision-makers within the medical profession for the treatment of AS. In addition, the registry data may also help to identifying areas for care improvement.

Current practice

Treatment guidelines, which summarise and evaluate available scientific evidence, are designed to assist healthcare physicians in selecting the optimal management strategies for an individual patient with a given condition. In 2012, the ESC/EACTS developed guidelines for the treatment and management of patients with VHD.¹⁵ In 2017, these guidelines were updated with new evidence on percutaneous interventional techniques and on risk stratification with regard to the timing of intervention of VHD.⁸ The task of developing these guidelines also includes the development of various tools, including condensed pocket versions, summary slides, booklets with essential messages and an electronic version for digital applications, to ensure that they are as widely adopted as possible. Despite these tools, however, early studies suggest that the implementation of and adherence to guidelines for the treatment of patients with AS still needs to be addressed. One study in patients aged 75 years or older suggested that surgery was denied in a third of patients with severe symptomatic AS, with the main unduly reasons for this decision being their advancing age and LV dysfunction rather than associated comorbidities as detailed in the guidelines.¹⁰ Another retrospective study, which also sought to understand if there were specific patient characteristics that impacted on the decision-making to treat symptomatic AS, revealed that 73 (69%) patients did not undergo AVR with the most common reason being cited that the patient's symptoms were not thought to be related to AS. With an average follow-up of 15 months, 15 (14%) of these 73 patients had died. The study concluded that physicians commonly under-recognise symptoms of AS and overestimated the operative risk, resulting in too few patients receiving a life-saving intervention.¹² Intervention is also recommended in selected patients with asymptomatic AS. Of the 5001 patients assessed in this study, 84 patients had severe asymptomatic AS, but stress testing was performed in only 6 (4%) patients and a decision to operate was made in 45 (54%) patients. The indications for surgery were in accordance with the American College of Cardiology/American Heart Association guidelines in 57 (68%) patients for AS, but the

decision to operate was frequently based on class IIb recommendations. The study concluded that intervention was 'overused' in 18 (21%) patients with AS and 'underused' in 9 (11%) patients with AS.¹³

The IMPULSE registry, which enrolled 2171 patients of hospitals with all treatment options (SAVR, TAVR, balloon aortic valvuloplasty (BAV)), showed a high rate of decision for conservative treatment in about a third of patients (31.1%). In 69% (n=1379) of the patients a valve replacement was chosen (66% TAVR vs 34% SAVR). Of these patients, the intervention was not performed within 3 months in 18.4% (n=254). By contrast, an intervention was performed in patients with asymptomatic AS in the absence of class I/IIa indication in a considerable number of cases (23% TAVR vs 17% SAVR). There was no clear decision pattern for this except a higher rate of reduced LVEF.¹⁴

To the best of our knowledge, there is no data on the impact of hospital type and adherence to treatment guidelines for patients with AS. For other cardiology conditions, a study in the USA comparing hospital treatment of patients with acute myocardial infarction showed that there was no significant difference between process measures and patient outcomes by hospital type or the availability of interventional capabilities.¹⁶ There is some evidence to show that the setting in which a cardiology patient is diagnosed may impact on their treatment and management, with patients being diagnosed in hospitals versus primary care being referred for more investigative procedures but this may be because patients who present to hospitals tend to have more symptoms and/or a higher disease burden.¹⁷ Again, to our knowledge, there is no comparable data on the medical location impacting the diagnosis or treatment of patients with AS.

Improved intervention

Factors which are associated with an increased risk of developing severe AS include patients who develop a rapid increase in aortic jet velocity and associated coronary artery disease.¹⁸ To help improve the treatment of severe AS, a better understanding of potential triggers in patients with asymptomatic AS that result in the rapid development of symptoms and multivariate predictors for developing severe disease are needed. The steps to diagnose AS are fairly well documented and include a physical examination and a transthoracic echocardiogram (including the assessment of various echocardiographic features to determine disease severity).¹⁹ Diagnosis, however, can be hampered by the presence of cardiac comorbidities such as coronary artery disease and particularly heart failure as well as lung disease.^{2-4 20} Assimilation of detailed data on the triggers of rapid disease progression, disease-associated risk factors and diagnostic procedures could be used to develop clinical care pathways for the treatment of patients with asymptomatic and symptomatic AS.

Pending issues

The IMPULSE enhanced registry was set up to establish the adherence to treatment guidelines and the identification, treatment and management of patients with AS in the primary, secondary and tertiary care settings. There are, however, various factors that the registry does not take into consideration. In some countries, such as the UK, a patient cannot select the hospital in which they would like to be treated. The IMPULSE enhanced registry records which physicians (eg, general practitioners and cardiologists) have referred patients to the hubs and satellite centres involved in the registry but does not consider country-specific nuances in hospital selection or that patients/patient families could have requested treatment at specific care institutions. It is possible that, for example, patients with more complex needs may choose larger hospitals due to the range of available treatments or the type of patient care offered. Similarly, hospital selection could be the result of its location/accessibility to the patient and their family.

The registry is currently set up to review patient care once at a medical institution but the findings of this registry may also help to provide guidance on treatment location based on the availability of treatment options/procedures and adherence to guideline recommendations. Secondary care centres, by their very nature, do not have access to surgical and percutaneous aortic valve interventions. It may be, for example, that patients with asymptomatic or mildly symptomatic AS could initially be seen at secondary care centres, while those presenting with severe symptomatic AS should be treated with more urgency and referred to tertiary care centres. This may also skew the data to suggest that, on paper, tertiary care centres have better adherence to treatment guidelines. Once all the registry data are available and analysed, it will be interesting to see if disease severity influences the final destination for patient care and, as a result, whether separate guideline recommendations need to be developed to accommodate this.

CONCLUSIONS

The aim of the IMPULSE enhanced registry is to provide high-quality data regarding the implementation and adherence to guidelines for the treatment and management of patients with AS in the primary, secondary and tertiary care settings. Information gained from this registry can be used to develop a clinical care pathway that can be applied across all patient services, irrespective of care facilities, to ensure that patients with AS receive optimal treatment and management in a timely manner. Overall, the hope is that the development of clinical care pathways that can be readily adopted by patient services will result in a reduction in morbidity and mortality associated with AS.

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Competing interests PB is the representative of the IPPMed, Cloppenburg, Germany. IPPMed has received research funding and honoraria for consultancy from Edwards Lifesciences. TKR, NF, ML, RPS and DM-Z received honoraria for advisory board meetings from Edwards Lifesciences. The institutions of these received funding for employing a study nurse.

Patient consent for publication Not required.

Ethics approval The registry is established in accordance with the Declaration of Helsinki (1964), and prior ethical agreements have been obtained from the appropriate ethics committee at each site. Prior to enrolment, patients are required to provide informed consent and data are collected by a co-ordinating nurse in the form of electronic case report forms (eCRFs).

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Data availability statement Data are available upon reasonable request.

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